REMARKS

Claims 1, 36, and 88 have been amended. Claims 27, 34, 80, 81, and 89 have been cancelled. Claims 1, 11, 34, 36, 42, 43, 82-88, and 90-93 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Objection of Claim 27

Claim 27 stands objected to on the ground that the claim is not further limiting because the independent claim already requires that the plurality of sequence be obtained from *Bacillus subtilis*.

Applicants have cancelled claim 27 rendering the objection moot.

II. The Rejection of Claims 1, 11, 34, 36, 42, and 43 under 35 U.S.C. § 112, Second Paragraph

Claims 1, 11, 34, 36, 42 and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on several grounds.

Ground 1: The Office Action states that the term "sub-inhibitory amount" in claim 1 is a relative term which renders the claim indefinite because the specification states that the subinhibitory amount is based on the MIC of the antimicrobial compound against a bacterium and cultivation of the bacterium, but there is no definition of an actual amount and one of ordinary skill in the art would only be reasonably apprised that the subinhibitory amount is based on the MIC of the antimicrobial compound against a bacterium. This rejection is respectfully traversed.

The term "sub-inhibitory amount" is defined on page 11, line 35, to page 12, line 3, of the specification. In the methods of the present invention, the bacterial cells are cultured in the absence and presence of at least one sub-inhibitory amount of an antimicrobial compound of interest. The sub-inhibitory amount is based on the MIC of the antimicrobial compound against a bacterium and cultivation of the bacterium at one or more concentrations below the MIC. The sub-inhibitory amount is preferably 0.5X MIC, more preferably 0.25X MIC, and most preferably 0.1X MIC. Consequently, there is a definition of an actual amount.

Ground 2: The Office Action states that the term "similarity or dissimilarity" is indefinite because pages 22-23 do not state a standard for determining similarity or dissimilarity, but rather discuss looking at expression profiles and determining similarity or dissimilarity and the

specification does not address the metes and bounds of what is similar or dissimilar and there is no criteria which defines how to determine whether something is similar or not. This rejection is respectfully traversed.

The term "similarity or dissimilarity" is defined on page 22, line 16, to page 23, line 2, of the specification. The methods of the present invention are used for determining a mode of action of an antimicrobial compound, by comparison with hybridization with a second nucleic acid sample obtained from the bacterial cells cultured in the absence or presence of a standard compound having a known mode of action. In this methods, the degree of similarity of the expression profiles is indicative of the similarity or dissimilarity of the mode of actions of the test compound and a known compound. Values are assigned to the hybridization complexes based on the relative amount of hybridization and the values are analyzed for the similarity or dissimilarity of the values to a second set of hybridization values assigned to the hybridization complexes formed from the second nucleic acid sample. A program for analysis, such as a computer algorithm, may be used to assign a mode of action for the test compound based on the degrees of similarity in the hybridization complexes.

The specification on page 22, lines 28-32, provides that when comparing the actions of different antimicrobial compounds, a similarity in the expression profile may mean that at least 1, preferably at least 5, more preferably at least 10, of the up-regulated arrayed genes commonly form hybridization complexes with the sample nucleic acid molecules at least once during a time course to a greater extent than would the nucleic acid molecules of a sample not treated with the test compound. The specification on page 22, lines 32-36, provides that similarity can also mean that at least 1, preferably at least 5, more preferably at least 10, of the down-regulated nucleic acid molecules commonly form hybridization complexes with the arrayed genes at least once during a time course to a lesser extent than would the nucleic acid molecules of a sample not treated with the test compound or a known toxic compound.

Consequently, the specification does state a standard for determining similarity or dissimilarity of a mode of action.

Ground 3: The Office Action states that the term "significantly different" in claim 36 is a relative term which renders the claim indefinite because there is no teaching of what types of detected levels of expression are deemed significantly different and what levels are not different and the specification does not disclose any criteria to determine these differences and does not provide a standard for ascertaining the requisite degree. This rejection is respectfully traversed.

The term "significantly different" is defined on page 23, lines 15-22, of the specification. Moreover, page 21, lines 18-21, of the specification provides that the difference in the detected

expression level is at least about 10% or greater, preferably at least about 20% or greater, more preferably at least about 50% or greater, even more preferably at least about 75% or greater; and most preferably at least about 100% or greater. Claim 36 has been amended to recite: "wherein the difference in the detected expression level is at least about 10% or greater".

Consequently, the specification does disclose criteria to determine these differences and does provide a standard for ascertaining the requisite degree.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

III. The Rejection of Claims 80-93 under 35 U.S.C. § 112, First Paragraph

Claims 80-93 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated:

> Neither the specification nor originally presented claims provides support for the method of determination wherein the plurality of sequences correspond to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *B. subtilis* cells. The specification nor originally presented claims provides support for the method of determination method wherein the difference in the detected expression level is about 10% to 100% or greater. Applicant did not point to support in the specification for a method wherein the plurality of sequences correspond to a percentage of the genome of the *B. subtilis* cells or wherein the difference in the detected expression level is about 10% to 100% or greater. Moreover, applicant failed to specifically point to the identity of the newly claimed method steps. Therefore it appears that the entire specification appears to fail to recite support for the newly recited method steps. At best pages 21-22 discuss data analysis, however the computational methods are used for the interpretation of microarray based expression profiles with include cluster analysis. The instantly recited claims are not drawn to microarray based expression profiles with include cluster analysis. Furthermore the instantly claimed methods do not require evaluating the results of the microarray statistical analysis to determine the significant of the differences in expression levels. Therefore, the claims incorporate new matter. Accordingly, it appears that there is no support in the specification. Therefore, applicants must specifically point to page and line number support for the identity of the method as recited by the newly added claims. Therefore, the new claims incorporate new matter and are accordingly rejected.

This rejection is respectfully traversed.

Applicants submit that the specification complies with the written description requirement. Support for the plurality of sequences corresponding to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *Bacillus subtilis* cell in claims 82-87 appears on page 13, lines 20-27, of the specification. Support for the difference in the detected expression level is at least about 10%, 20%, 50%, 75%, and 100% or greater appears on page 21, lines 11-21, of the

specification. Consequently, the previously added claims do not incorporate new matter.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

IV. The Rejection of Claims 80-81 under 35 U.S.C. § 101

Claims 80-81 stand rejected under 35 U.S.C. § 101 on the ground that the claimed invention is directed to non-statutory subject matter. The Office Action stated:

> In the instant case, the claims are drawn to a program for analysis wherein the program comprises a computer algorithm. Moreover, the instant claims are not drawn to functionally descriptive material recorded on some computer-readable medium, nor does the program have any actual components thereby making the program structurally and functionally interrelated to the method. The instant claims are to a computer algorithm that does nothing more than solve mathematical problems or manipulate abstract ideas or concepts. Thus, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process. In practical terms, claims define nonstatutory processes if they: consist solely of mathematical operations without some claimed practical application i.e., executing a "mathematical algorithm" See *Schrader*, 22 F.3d at 294-95,30 USPQ2d at 1458-59.

Claims 80-81 have been cancelled rendering the rejection moot.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 101 and respectfully request reconsideration and withdrawal of the rejections.

V. The Rejection of Claims 1, 11, 34, 36, and 42 under 35 U.S.C. § 103

Claims 1, 11, 34, 36, and 42 under 35 U.S.C. § 103 as being unpatentable over Zhang *et al.* (*Gene* 255: 297-305, 2000) in view of Kunst *et al.* (*Nature* 390: 249-266, 1997). The Office Action stated:

> [i]t would have been prima facie obvious at the time of applicants invention to exchange the gram-positive bacteria as taught by Zhang et al., used within the method for determining the mode of action of an antimicrobial compound, comprising a detection of hybridization complexes, a comparison of the hybridization complexes to a standard compound having a known mode action, and assigning a mode of action for the unknown antimicrobial compound based on the similarity or dissimilarity of values assigned to the hybridization complexes detected from the known sample for the gram-positive *Bacillus subtilis* bacteria as taught by Kunst et al. No more than routine skill would have been required to exchange an equivalent and functionally alternative gram-positive bacteria for another for use in a method of determination. Thus one would have a reasonable expectation of success since the prior art already teaches that *Bacillus subtilis* is an ideal regulated gene expression system.

This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the *claimed subject matter as a whole* would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere*, 383 U.S. 1 (1966).

Zhang *et al.* disclose that three regulated promoter systems, previously developed in *Bacillus*, all function and exhibit titratable induction in *Staphylococcus aureus*, which together provide physiologically relevant protein expression levels of over three orders of magnitude. Zhang *et al.* also disclose that the chromosomally-integrated Spac system, in combination with the LacI-expressing plasmid pFF40, provides an inducible, titratable and well-regulated system for testing the requirement of specific gene products for cell viability and creating conditional lethal phenotypes in *S. aureus*. Zhang *et al.* further disclose that strains with titratable gene products are useful for linking the antibacterial activity of an antibiotic with the proposed target mechanism.

Kunst *et al.* disclose the complete genome sequence of *Bacillus subtilis*.

It is well established that focusing on individual elements of the claimed invention, rather than on the invention as a whole, is not the proper test under 35 U.S.C. § 103. *Environmental Designs v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983). The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." *Lindemann Maschinefabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d at 1462, 221 USPQ at 448.

With regard to rejections under 35 U.S.C. 103, the law requires, when relying on a combination of prior art references to render a claimed invention obvious, that the prior art references contain within them a suggestion of the possibility of achieving the improvement of the claimed invention, such a suggestion being either express or implied. *In re Semaker*, 217 USPQ 1 (Fed. Cir. 1983). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *Carella v. Starlight Archery*, 231 USPQ 644 (Fed. Cir. 1986). It is also impermissible to use the claims as a framework from which to pick and choose among individual references to recreate the claimed invention. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). A reference, or references, must show or suggest the properties and results of the claimed invention, or suggest the claimed combination as a solution to a given problem, in order

to successfully be relied upon for an obviousness rejection. *In re Wright*, 6 USPQ2d 1959 (Fed. Cir. 1988). The mere fact that prior art references could be readily modified to form the claimed invention is not sufficient either, since the mere fact that the prior art could be modified would not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Laskowski*, 10 USPQ2d 1397 (Fed. Cir. 1989).

Applicants submit that Zhang *et al.* is irrelevant to the claimed invention. The present invention relates to method for determining the mode of action of an antimicrobial compound, comprising: (a) detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing cells of a *Bacillus subtilis* in the presence of at least one sub-inhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequences corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected, compared with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode of action, is indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound; and (b) assigning a mode of action for the antimicrobial compound based on the similarity or dissimilarity of values assigned to the hybridization complexes detected in (a) based on the relative amount of hybridization to a second set of hybridization values assigned to the hybridization complexes formed from the second nucleic acid sample.

Zhang *et al.* teach three regulated promoter systems in *Staphylococcus aureus* (*Xyl*/tet, Xyl, and *Spac*) that exhibit titratable induction covering a range of gene expression of approximately 3000-fold. They show that one of the promoter systems, the *Spac* system, is useful for examining gene essentiality and creating specific conditional lethal phenotypes. Zhang *et al.* suggest that titration of selective target gene products using this system allows direct demionstration of antibiotic mode of action. An an example, Zhang *et al.* examined whether the cellular antibacterial activity of a hydroxamic acid inhibitor (designated SB220334) of the *S. aureus* Pdf1 enzyme activity was due to its direct action on the *S. aureus* enzyme by constructing a *S. aureus* strain, called FFdef1, in which the P_{spac} promoter was inserted immediately upstream of the *def1* gene encoding Pdf1 and a Lac1-expressing plasmid pFF40 was introduced into the strain. The antimicrobial activity of compound SB220334 against *S. aureus* Ffdef1 (pFF40) was examined in media containing varying concentrations of inducer. The results demonstrated a clear correlation between MIC values and the levels of induction

suggesting that the antibacterial activity of SB220334 appears to be due to its inhibition of the Pdf1 target enzyme.

Consequently, Zhang *et al.* teach a method for evaluating whether a compound with antibacterial activity directly acts on the product of a specific gene which is selectively regulated by the P_{spac} promoter under inducing conditions, but do not teach or suggest the instant invention, as claimed. The claimed method and the method of Zhang *et al.* involve different techniques.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 103 and respectfully request reconsideration and withdrawal of the rejections.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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